REMARKS/ARGUMENTS

I. Status of Claims

Claims 1-3, 17-19 and 21-22 are pending.

Claims 4-16 and 20 are withdrawn

II. Neither Rose, Malorny Nor Geysen Teach All the Claim Elements, and "Inherency" Does Not Remedy Omission of Elements in the Publications.

The examiner is continuing to pull out peptides from the literature and try to force them into the criteria of claim 1. However, based upon the elements of this invention, and application of the elements to the cited references of Rose, Malorny and Geysen, it is quite clear that none of the latter references, nor the peptides cited therein, fit the criteria of claim 1. Furthermore, not only do the cited peptides from Rose, Malorny or Geysen not fit claim element 1 (d) and 1 (e) as the examiner admits, but neither do they fit claim 1 (c) which requires:

> (c) a net hydrophilic structure as determined by the amino acid sequence of the peptide, said structure located on the surface of the target protein;

As clearly provided in the specification, for example on page 4 Step 5, the rolling sums of squares method is used to determine if a peptide satisfies 1(c). A hydrophilic peptide is assembled by amino acids after determining the hydrophilic index of each constituent amino acid, based upon the sum of 7 rule relying on the 7 consecutive amino acids that precede and follow each amino acid comprising the peptide in question. (Exhibit A, yellow boxes). Not only has the examiner not shown express teaching of 1(c) in the publications cited, but the selected peptides do not satisfy 1(c). As shown in Exhibit A, the peptides of Geysen (peptides having both green and pink boxes are those cited by the examiner), are not hydrophilic, not all yellow, so these peptides would not be completely on the surface of the protein as required by 1(c). (see explanation in section II. C herein).

Additionally, as the examiner admitsm the peptides of Rose, Malorny and Geysen do not comply with claim 1, sections (d) and (e), because they show sequence homologies with comparative proteins that raise the possibility of producing antibodies that are not specific for the intended target protein.

It is not a basis for rejection that some of the peptides of Rose, Malorny and Geysen have a net hydrophilic character because the essential additional feature of uniqueness of the peptide sequences to the target protein is not satisfied; ie, the invention specifies that the net

hydrophilic peptide characteristic must be coupled with uniqueness to the target protein as discerned by careful examination of all other available relevant comparative protein sequences.

These sequences are either: (1) buried in the interior of the derivative protein [not satisfying 1(c)] and are physiologically useless for diagnostic or therapeutic consideration or (2) are located on the protein surface but are not sufficiently exclusive to the targeted protein or targeted organ or targeted microorganism/virus for use in either diagnostic or therapeutic applications.

A. Rose *et al.* (WO97/12042) does not anticipate Claims 1-3, 17-19 and 21

The examiner asserts that peptides related in Rose *et al.*,

RGMTEAA and

RGLTESA

anticipate claims 1-3, 17-19 and 21 under 35 U.S.C. §102(a). The examiner, not Rose *et al.*, equate Glass III (Class III?) of glycoprotein B with a target protein of the present claims (citing Table 8, Class III, p. 47, of Rose *et al.*). However, Rose *et al.*, does not express the term "target protein."

The examiner admits that Rose *et al.*, does **NOT** teach a "comparative protein" and then mistakenly relies on "inherency" to supply this missing key element of the present claimed invention (Office Action, page 3).

The examiner provides no legal support for his assertion that it is "the burden of applicant" to show Rose et al." does not possess the recited features of *ANY* comparative protein compared to the plurality of immuogenic peptides taught by Rose et al.".

B. Claims 1 and 3 are not anticipated by Malorny *et al.*

The examiner asserts that "a plurality of peptides" of what the examiner decided were "target proteins," namely "Opa target proteins a*Nesseria* (*sic*) . . . "citing Introduction, page 1323, left column, inherently possess the characteristics of claim 1(d)(e). The examiner states

> that the burden is on applicant to show that there is NO comparative protein with respect to the plurality of peptides disclosed by Malorny *et al. (emphasis added).*

With due respect, the examiner is confused. There should be comparative proteins because they are defined as similar and must be differentiated from a target protein.

Malorny's peptides are those used to produce mouse monoclonal antibodies. Mouse monoclonal antibody development does not adequately predict diagnostic or therapeutic

applications in either human or veterinary conditions. Rather, such antibodies need to be screened against the target protein and compared to any reactivities to other (comparative) proteins. It is not technically feasible, to screen any antibody reagent against ALL other comparative proteins because they are not available. In contrast, the specification of this invention provides the method to select relevant peptides that will yield reactivities to antibodies that are SPECIFIC to the target protein using algarithms and computer data bases, rather than mere trial and error - just generating antibodies without specificity.

Furthermore, none of the peptides cited in Malorny are specific when analysed as defined in the specification, i.e., to target proteins, as

The sequence GKATQ is also found on the outer surface of the human gut colonizing bacterium, *Enterococcus faecalis* on its alpha-1, 2-mannosidase protein and thus Specific microorganism diagnosis is not facilitated for *Neisseria M.* Additionally, the KGATQ sequence for immunization would be excluded from consideration by the methods of this specification because such immunization may result in reduction in number or eradication of the *Enterococcus faecalis* bacterium in the colon, one of the three principal colonizing bacteria. Its loss would result in alteration of the micro-organism balance between the various enteric bacteria with resulting morbidity or mortality of the host.

Furthermore, the examiner needs to realize that the Malorny's publication is principally directed toward tying together the organismal commonality (*Neisseria*), **not** to differentiate between different species, or locate differences within species by specific epitope variability. In contrast, The methods and claims of the present specification define how to select peptide sequences, and to detect antibody reactivities to such sequences, that are SPECIFIC to a particular protein, the target protein.

All of the other peptide sequences cited in Malorny do NOT satisfy the claims of this specification; because they are not specific.

The peptide sequence of KESNYS is also found on outer surface of 5 human proteins:

Kinase (PRKA) anchor protein 9 with the sequence of as KESNY;
Serine/threonine-protein kinase LATS1 as KESNY;
Splice variant AKAP350 as KESNY;
Large tumor suppressor 2 as KESNY;
Centrosome- and Golgi-localized PKN-associated protein as KESNY.

The peptide sequence of PSGSTT is also found on human:

PHD finger protein 22 as PSGSTT;
BCL6 co-repressor-like 1 as PSGSTT;

The peptide sequence of PTKGAT is also found on human:

Spectrin beta isoform b as KPTKG;
Retinoic acid induced protein 1 as KPTKG;
Protein MGC39633 as KPTKG;
Myosin heavy chain as KPTKG;
Modulator of estrogen induced transcription isoform a as KPTKG;
Zinc finger protein 198 as PTKGA;

The peptide sequence of PTKGATQP is also found on human:

Proteins displaying homology with PTKGAT (above);
Protein BAC86519 as KAGATQ;

All of the above homologies clearly demonstrate the differences of the invention of this specification as compared to Malorny (and the other references cited by the examiner as noted both above and below), as well as the uniqueness of the invention and claims of this specification.

Furthermore, most of the peptides listed by Malorny as being immunologically useful are located in the molecular interior of the Opa protein and are therefore would not useful for producing specific antibodies as specified in claim 1.

Again the examiner invokes "inherency" to substitute for the omission of compliance with claim 1, elements (d) and (e), which the examiner admits are not possessed by the "plurality of peptides" of Malorney, who did not ascertain specific antibody reactivity. Moreover, as shown clearly above, the structures of the peptides used in the Malorny reference are is not unique to *Neisseria*. All would have been excluded by the present inventors because antibodies to them would damage humans.

C. Claims 1 and 3 are rejected under 35 USC § 102(b) over Geysen *et al.*, (US 5595915).

The examiner justifies this support for a 102(b) rejection of claims 1 and 3 as

> Geysen et al., teach a plurality of peptides for identifying A-type foot and mouth disease virus (FMDV) protein.

and lists alleged characteristics of "the peptides" - again invoking "inherency" to supply missing compliance of Geysen's peptides, with the present claim 1 (d) and (e).

The goal of Greysen was to synthesize a plurality of overlapping peptides and test them to find antigenic sites. Exhibit A shows why the Geysen peptides, for example, do not anticipate claim 1. The left hand column lists amino acid position from 720-777 and 846-895

respectively of the "hoof and mouth" virus (FMDV) protein (Geysen examined only a 213 amino acid fragment, the salient part of which is included in Exhibit A).

The column to the far right lists the amino acids, gives net hydrophilicity as determined by the sum of 7. Only positive numbers are hydrophilic and on the surface of the protein.

The yellow boxes delineate net hydrophilic values for peptides. The green boxes are the corresponding peptide regions. The pink are non-hydrophilic. The middle shows peptides of Geysen - note they are pink and green, not satisfying claim 1(c).

D. Legal Criteria for Inherency Are Not Satisfied in the Arguments in Support of 35 USC § 102(b) rejections.

According to James O. Wilson, Supervisor Patent Examiner, Technology Center 1600, USPTO, 2004

> To establish inherency the extrinsic evidence must make clear that the missing descriptive matter is necessarily present in the thing described in the alleged anticipatory reference.
>
> The examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the alleged inherent characteristic necessarily flows from the teachings of the applied prior art.

The examiner has not satisfied these directions.

An anticipating prior art reference should disclose ***each and every limitation of the claim*** expressly or inherently. *Akamai Techs. v. Cable & Wireless Internet Servs.*, 344 F.3d 1186, 1192 (Fed. Cir., 2003). To anticipate a claim, ***a reference must disclose every element of the challenged claim*** and enable one skilled in the art to make the anticipating subject matter. *PPG Industries, Inc. v. Guardian Industries Corp.*, 75 F.3d 1558, 1566, 37 USPQ2d 1618, 1624 (Fed. Cir. 1996) *(emphasis added)*.

The examiner admits that all claim elements are **not** present in the 3 cited publications (Malorny, Geysen and Rose). The examiner provides no support for invoking "inherency" to supply what he admits are missing elements (d) and (e) in the peptides reported in the publications discussed in II. A-C herein.

To establish inherency, the process or composition or the missing element must have existed or occurred to a certainty **(i.e., not possibility or probability)**. *Scaltech, Inc. v.*

Retec/Tetra, LLC., 178 F.3d 1378, 1384, 51 U.S.P.Q.2D (BNA) 1055, 1059 (Fed. Cir. 1999).

(emphasis provided)

> We do not regard the accidental formation of fat acid in Perkin's steam cylinder from the tallow introduced to lubricate the piston (if the scum which rose on the water issuing from the injection pipe was fat acid) as of any consequence in this inquiry. What the process was by which it was generated or formed was never fully understood. Those in the art of making candles or in any other art in which fat acids are desirable, certainly never derived the least hint from this accidental phenomenon in regard to any practicable process for manufacturing such acids.
>
> If the acids were accidentally and unwittingly produced, whilst the operators were in pursuit of other and different results, without exciting attention and without its even being known what was done or how it had been done, it would be absurd to say that this was an anticipation of Tilghman's discovery.

Tilghman v. Proctor, 102 U.S. 707; 26 L.Ed. 279 (Sup. Ct. 1880).

> An accidental or unwitting duplication of an invention cannot constitute an anticipation. *In re Felton*, 484 F2d 495, 500, 179 U.S.P.Q. 295, 298 (C.C.P.A. 1973).

If something happens only occasionally, it is not grounds for anticipation as "occasional results are not inherent". *MEHL/Biophile Int'l Corp., v. Milgraum*, 192 F.3d 1363, 1365; 52 U.S.P.Q. 2d 1301 (Fed. Circ. 1999) at 1365. In the present case, even if peptides in the art fell within the scope of claim 1 occasionally, which the examiner has **not** shown, they would not anticipate.

In regards to a machine, the Supreme Court held that the claims were not anticipated by a machine in the art:

> In administering the patent law the court first looks into the art to find what the real merit of the alleged discovery or invention is and whether it has advanced the art substantially...In the case before us, for the reasons we have already reviewed, we think that Eibel made a very useful discovery which has substantially advanced the art.
>
> ...In the first place we find no evidence that any pitch of the wire, used before Eibel, had brought about such a result as that sought by him, and in the second place, if it had done so under unusual conditions, accidental results, not intended and not appreciated do not constitute anticipation. *Tilghman v. Procter*, 102 U.S. 707, 711; *Pittsburgh Reduction Company v. Cowells Electric Company*, 55 Fed. 301, 307; *Andrews v. Carmen*, 13 Blatchf. 307, 323.

Although the claimed composition was intended and recognized in the art, the result the composition could achieve was unintended and not recognized in the art. The result the composition could achieve in the art had a different purpose.

In another case, claims were directed to Element 95, now known as Americium. The inventors discovered this element and attempted to patent it. The art applied against the claims was Americium produced in the Fermi process for producing uranium in a reactor. Apparently, using the Fermi process in a reactor to produce uranium inherently produces Americium.

The Federal Circuit, however, held that there was no anticipation. The Court stated that the reactor could not have produced any more than "a billionth of a gram," which would have been distributed throughout forty tons of intensively radioactive uranium reactor fuel. As the Court stated, "this amount of an unknown unconcentrated isotope, if present, would have been undetectable."

> If the earlier disclosure offers no more than a starting point for further experiments, if its teachings will sometimes succeed and sometimes fail, if it does not inform the art without more how to practice the new invention, it has not correspondingly enriched the store of common knowledge, and is not an anticipation.

In re Glenn T. Seabor, 328 F.2d 996; 14 U.S.P.Q. 662 (C.C.P.A. 1964)

Where an intermediate was the same as an embodiment of the invention, the Court found no anticipation, citing *Tilghman* and *Eibel.*

> ...We do not disagree with the Board's apparent conclusion that an intermediate structure for the Sands device could possess the characteristics called for in these claims. However, in view of the purpose for which the Sands device was intended, it is apparent that it requires no critical dimension which would lead to a structure inherently having those characteristics. Therefore, it would be mere happenstance if any structure made according to Sands met the limitations of the claims. An accidental or unwitting duplication of an invention cannot constitute an anticipation. *Tilghman v. Procter* 102 U.S. 707 (1880); *Eibel Process Co.v. Minnesota and Ontario Paper Co.* 261 U.S. 45 (1923). *(emphasis provided).*

In *Continental Can Company U.S.A. Inc. v. Monsanto Company, 948F2d 1264, 1266 (Fed. Cir. 1991)* the Federal Circuit noted that the reference would anticipate only if hollow

ribs were necessarily present and the person of ordinary skill in the art would have recognized that the ribs were hollow.

> To serve as an anticipation when the reference is silent about the asserted inherent characteristic, such gap in the reference may be filled with recourse to extrinsic evidence. Such evidence must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, *and that it would be so recognized by persons of ordinary skill. (emphasis provided).*

In conclusion, the examiner merely invoking "inherency" without further support, is not a legally sufficient basis for rejection of claims in the present application.

III. Comparative Proteins are Definite in the Specification

FIG. 2 a and b were discussed during the interview of April 13, 2005 where it was specifically pointed out what were comparative proteins - "those most closely matching the linear amino acid sequence of the *Helcobacter pylori* flagella sheath adhesion protein sequence using the BLAST amino acid sequence homology comparison program on the National Library of Medicine website [www.ncbi.nlm.nih.gov:80/BLAST]. FIG. 2b has a light box "likely to serve as a functionally specific antigen when compared to the two aligned, comparative protein amino acid sequences using the selection criteria of the disclosed invention."

The other FIGS. show the final tests - some candidate peptides satisfied the criteria - some didn't! "Thus confirming the need to test specific functional utility (immunogenic) of the peptide antigen." (p. 11, lines 31-32 (see also Example 1).

The examiner complains that the term "comparative proteins" is:

> vaguely, or alternatively broadly, defined in the specification; any "non-target" protein is a "comparative protein."

citing only to 0010 and 0012 which is erroneous. The examiner's position totally ignores the extensive support and guidance in the specification for the term "comparative protein," which applicant previously supplied for the record.

In the specification, the details for defining "comparative protein" are listed many times as for example in the following chart:

Page	Lines	Comments (emphasis provided)
2	21 – 23	"peptides of the present invention are **functionally specific,** (*emphasis provided*) they are **not structurally** specific, because the peptides match not only amino acid sequences of

		target proteins, but also **to some degree** match sequences of non-target proteins"
2 3	35 – 36 1	"peptides of claim 1 regions on selected non-target proteins (the "comparative proteins")
3	23 – 26	to comply with claim 1, search for all available sequence matches of non-target proteins, select at least one of the proteins that shows some degree of homology to the target protein select amino acid sequences of at least 4 in length
4	Step 5	for claim 1(c) - hydrophilic "use the rolling sum analysis of 7 constructive residues (Hopp et al, 1981; Parker et al., 1986; Fauchere and Pliska, 1990)."
4	Step 7	"analyze 'comparative proteins' for possible amino acid sequence **similarity** to...the target molecule..."
4	Step 8	select peptides which are 50% or less homologous with peptide regions of comparative protein amino acid sequences
4	Step 9	Reject peptides of Step 8 with 4 or more contiguous amino acids **identical** to a contiguous sequence of the comparative proteins
5	6 – 34	Reiterates steps of claim 1 - "non-target, (non-specific) proteins" are compared (using e.g. BLAST) to candidate peptides to see if the peptides fit criteria of claim 1. "Functionally specific peptide antigens are selected on the basis of having no more than 50% amino acid matching (sequence homology) with the comparative protein peptide sequences." The goal is to select peptides which will **not** generate antibodies to comparative proteins, but will be selective for target proteins.
6	7 – 10	Comparative proteins (not expressly stated here but see claim 1(d) are "single non-target proteins; that is proteins comprising non-targeted microorganisms, or proteins comprising non-targeted tissues"
8	32-35	Defines "Functionally specific" and "targeted"
10	29 – 34	FIGS. 1 and 2.
11	1 – 15	FIG. 1 shows where the hydrophilic portions of the sequence of a target protein, are bold and underlined; FIG. 2a shows a comparison between one of those peptides aligned with "closely matched peptide sequence of two comparative microorganism proteins," the comparative proteins were selected by BLAST as "those most closely matching the linear amino acid sequence of the target protein."

		the peptide must fit other criteria to be suitable.
11	6 – 15	FIG. 2B shows alignment of target protein sequences with comparative protein sequences (see amended specification).

The specification also clearly defines the method for obtaining comparative proteins: Those of skill in the art know how to access BLAST (specification, page 2, lines 20-23; page 3, lines 23-26; page 5, lines 13-18; page 10, FIG. 2a; page 12, lines 29-36; page 13, lines 1-2) to search the Protein Data Base for comparative proteins of the present application as instructed in the specification. They would assess the routine in BLAST for "short, nearly exact matches to the target protein." The results would be inspected to select comparative protein specimens.

In order to find peptides that are specific for target proteins and **not** for close structural proteins from the same species, the inventors found how to select peptides from among those somewhat structurally similar to target proteins, but functionally different, where "function" means producing antibodies specific for the target protein - antibodies that can ferret out target proteins from among "comparative" i.e. non-target proteins.

The inventors have found that by following steps 1-9 (pages 3-4) candidate peptides are identified and synthesized (step 10) which are similar but not identical structurally to proteins that could be mis-classified as target proteins, but functionally should be specific for the target protein because of the selection method.

The final (step 11) is to show that the synthesized candidate peptides are able to detect the target test protein in the midst of comparative proteins. If **not,** the candidate peptides are discarded (step 11).

The purpose of the comparative proteins is to avoid selecting peptides that functionally will not distinguish between target and comparative proteins.

Contrary to the examiner's assertion on page 3, the product of claim 1 is not "the same product . . . taught by the prior art" therefore, the entire argument from Office Action page 3 ("The production of product by a particular process . . .") to page 4 (. . . [footnote omitted.}) is irrelevant.

Applicant has no idea where the examiner gets the idea that the invention is a "fragment or part of a non-target "comparative protein". It is not. Comparative proteins are not claimed.

IV. A Prima Facie Case of Obviousness is not Established

Claim 22 was rejected under 35 U.S.C. §103(a) over Rose et al. together with Michael

et al. (US4469677).

The examiner admits that Rose *et al.* does not teach "prescribing the peptide as a desensitizing agent for therapy purposes," and invokes Michael *et al.* who "review a conventional method of administering identifying antigen to the host to *desensitize*..." but **no** teaching or motivation is alleged to combine Rose *et al.* with Michael *et al.*

Furthermore, even if combined, given the deficiencies in Rose *et al.* discussed in II. A. herein, the combination would not yield the present invention.

In *Nursery Supplies*, the court held:

> One **cannot simply backtrack from the invention to find a connection** to the prior art. Hindsight must be avoided. See *W.L. Gore and Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540 (Fed. Cir. 1983). Rather, **one must start with the prior art and find some suggestion or motivation either in a single reference** to modify it to produce the claimed invention, or some suggestion or motivation in a group of references to combine them to produce the claimed invention. *Nursery Supplies v. Lerio Corp.*, 45 U.S.P.Q.2d (BNA) 1332 (M.D. Pa. Sept. 19, 1997). (*emphasis added*).

There is no teaching or suggestion to combine Rose and Michael. Even if Rose and Michael were properly combined, the combination does not produce claim 22 because Rose does not teach or suggest immunogenic peptides that fit the description of claim 1, and Michael only teaches administration. Furthermore, the invention of this specification teaches that the peptides identified by the methods of the claims are to be used for therapeutic purposes. Neither Rose nor Michael, nor the other references cited by the examiner fit the criteria of the selection of the relevant peptides of this invention.

It is to be noted, however, that citing references which **merely indicate that isolated elements and/or features** recited in the claims are known **is not a sufficient basis** for concluding that the combination of claimed elements would have been obvious. *Ex parte Hiyamizu* (BPAI 1988) 10 PQ. 2d 1393 (*emphasis added*).

Even if all of the elements of a claim are present in the prior art, the claim will not be obvious unless the prior art also contained, at the time the claim was filed, a motivation to combine prior art elements into the claimed invention. The conclusion that the prior art contained a motivation to combine is a conclusion of fact. *Scimed Life Sys. v. Johnson & Johnson*, 2004 U.S. App. LEXIS 510.

Obviousness requires **a suggestion of all limitations** in a claim." *CFMT, Inc. v. YieldupInt'l Corp.*, 2003 U.S. App. LEXIS 23072 (Fed. Cir. 2003) (*emphasis added*).

To properly combine two references to reach a conclusion of obviousness, there must be some teaching, suggestion or inference in either or both of the references, or knowledge generally available to one skilled in the art, which would have led one to combine the relevant teachings of the two references. *Ashland Oil, Inc. v. Delta Resins and Refractories, Inc. et al.* (CAFC 1985) 776 F. 2d 281, 227 USPQ 657; *Ex parte Levengood, supra.* Both the suggestion to make the claimed composition or device or carry out the claimed process and the reasonable expectation of success must be founded in the prior art, not in applicant's disclosure. *In re Vaeck* (CAFC 1991) 947 F. 2d 488, 20 PQ. 2d 1438. The references, viewed by themselves and not in retrospect, must suggest doing what applicant has done. *In re Shaffer* (CCPA 1956) 229 F. 2d 476, 108 USPQ 326; *In re Skoll* (CCPA 1975) 523 F. 2d 1392, 187 USPQ 481.

In *re Rouffet,* the court held

To prevent the use of hindsight based on the invention to defeat patentability of the invention, this court **requires the examiner to show a motivation to combine the references that create the case of obviousness.** In other words, the examiner must show reasons that the skilled artisan, confronted with the same problems as the inventor and with no knowledge of the claimed invention, would select the elements from the cited prior art references for combination in the manner claimed. In *re Rouffet,* 149 F.3d 1350 (Fed. Cir. 1998). (*emphasis added*).

Therefore, Claim 22 is not obvious over in view of Rose and Michael.

IV. Other Issues

Because new grounds of rejection are given (Action, page 7), applicant requests removal of finality.

Claim 1, step (d) is amended to remove "the part of the comparative protein."

V. Conclusion and Summary

In view of the arguments presented herein, please allow all pending claims. No fees are believed due at this time, however, please charge any additional deficiencies or credit any overpayments to deposit account number 12-0913 with reference to our attorney docket number (21417/92378).

Respectfully submitted,

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EXHIBIT A

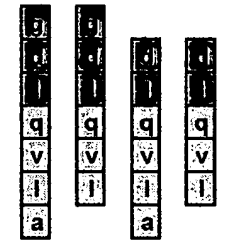
AA Position		Net Hydrophilic (Rolling Sum)
720	k	-3
721	a	-2
722	p	2.8
723	f	0.8
724	t	-3
725	r	-4
726	l	-4
727	a	-4
728	l	-4
729	p	-7
730	y	-5
731	t	-5
732	a	-1
733	p	-2
734	h	-2
735	r	-2
736	v	-2
737	l	-3
738	a	-5
739	t	-5
740	v	-3
741	y	-2
742	d	-1
743	g	2
744	r	1.2
745	n	3.8
746	k	0.3
747	r	0.6
748	s	4
749	a	4.1
750	s	4.1
751	d	6.7
752	s	6.4
753	r	9.9
754	s	7.8
755	g	4.8
756	d	4.8
757	l	0
758	g	-1
759	s	-1
760	i	-1
761	a	-1
762	a	-1
763	r	-2
764	v	-0
765	a	-1
766	t	-1
767	q	-4
768	l	-3
769	p	-5
770	a	-4
771	s	-7
772	f	-5
773	n	-5
774	y	-7
775	g	-7
776	a	-5
777	i	-5

Hydrophilic

Geysen, not 1(c)

EXHIBIT A

AA Position	Net Hydrophilic (Rolling Sum)	
846 p	-2	
847 h	-2	
848 r	-2	
849 v	-2	
850 l	-3	
851 a	-5	
852 t	-8	
853 v	-6	
854 y	-4	
855 n	-5	
856 g	-1	
857 n	-2	
858 c	0.1	Hydrophilic
859 k	2.9	
860 y	3.2	
861 g	3	
862 e	2.5	
863 s	-1	
864 p	1.6	
865 v	0.1	
866 t	0.1	
867 n	-0	Hydrophilic
868 v	2.8	
869 r	2.5	
870 g	3.1	
871 d	1.4	
872 l	1.1	
873 q	-2	
874 v	-2	
875 l	-2	
876 a	-1	
877 q	-2	
878 k	2.9	
879 a	4.3	
880 a	3	
881 r	2.8	
882 t	-1	
883 l	0.2	
884 p	-2	
885 t	-5	
886 s	-6	
887 f	-5	
888 n	-5	
889 y	-7	
890 g	-4	
891 a	-2	
892 i	-2	
893 k	2.8	Hydrophilic
894 a	1.3	
895 t	1.4	



Geysen, not 1(c)